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Behavioral Outcomes of 4-year-old Children Prenatally Exposed to Methadone or Buprenorphine: A Test of Three Risk Models

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Abstract

It is still under debate whether the reported effects of opioid maintenance therapy (OMT) on child behavior are a direct effect of prenatal exposure, or whether other factors are involved. This prospective cohort study investigated three models; the teratogenic risk model, the maternal risk model, and a combined risk model in a group of 35 children (M = 52.20 months, SD = 1.69) prenatally exposed to OMT. Results revealed support for the maternal risk model and the combined model, with the combined model predicting child internalizing and externalizing behavior problems the best (R^2 = .65, p = .008 and R^2 = .74, p = .003, respectively). Findings suggest that behavior problems in children of women in OMT may not be a direct exposure effect. This underscores the importance of taking into consideration multiple factors when studying the effects of prenatal OMT exposure on child behavior.

Keywords

Child behavior, prenatal exposure, methadone, buprenorphine, opioid maintenance therapy

Introduction

Since the 1960s, methadone has been prescribed to pregnant opioid dependent women in order to reduce illicit drug use and improve perinatal outcomes (Brown et al., 1998). More recently, buprenorphine has also been recommended as treatment for opioid-dependent pregnant women (Jones et al., 2010). Compared to opioid-dependent women who do not receive substitution treatment, pregnant women in opioid maintenance therapy (OMT) programs take better care of their health, have better treatment attendance, and are less likely to use illicit substances or engage in other risk behaviors (Fischer et al., 2000). Despite these advantages, various behavioral problems have been observed in children of women in OMT. At 12 months, differences in attachment behavior have been observed between control infants and infants prenatally exposed to methadone with methadone-exposed infants displaying higher levels of disorganized attachment behavior, lower levels of contact maintenance, and higher levels of avoidance (Goodman, Hans, & Cox, 1999). At age 2½, methadone and buprenorphine exposed children show more internalizing and externalizing behavior problems compared to non-exposed children (Sarfi, Sundet, & Waal, 2013). At 4 years old, they struggle with less efficient executive functions compared to their non-exposed peers (Konijnenberg & Melinder, 2014). In preschool age, children of women in OMT are more aggressive, more depressed, less responsive, and have more difficulties with interactions with peers and adults compared to non-exposed children (Baar, Soepatmi, Gunning, & Akkerhuis, 1994; Salo et al., 2009). When reaching school-age, methadone-exposed children more often require special assistance for behavioral and academic problems than non-exposed children (Rosen & Johnson, 1985).

On this background, there is reason to believe that children of women in OMT experience more behavioral problems than their peers. However, the evaluation of the effects of prenatal methadone and buprenorphine exposure is complicated by the fact that exposure to methadone or buprenorphine is only one of the factors that can influence child development. Therefore, it has been suggested that prenatal drug exposure should be studied as a risk factor within a developmental perspective (Moe & Slinning, 2002).The environment in which children are raised influences their experiences, which in turn affects brain development (Greenough, Black, & Wallace, 1987). The effects of prenatal drug exposure on children's development should therefore be evaluated in light of possible associations between exposure status and related psychosocial factors. Children with one or both parents in OMT are often raised in families characterized by single parenthood, social isolation, financial difficulties, high levels of (maternal) depression and anxiety, and illicit drug use (Dawe, Harnett, Rendalls, & Staiger, 2003; Fiks, Johnson, & Rosen, 1985; Kolar, Brown, Haertzen, & Michaelson, 1994). Child abuse and neglect is not uncommon in families where one or both parents are in OMT (Kolar et al., 1994). Children of women in OMT may therefore be exposed to both teratogenic and family risk factors. Current research suggests that OMT is the best treatment option for most pregnant women with opioid-dependence. However the safety of OMT during pregnancy is still under debate (McCarthy, 2012), and it is essential to study whether the reported long-term effects on children's behavior are a direct effect of prenatal exposure, or whether other factors, such as maternal health or stress

also account for the differences between exposed and non-exposed children. Insight into the relative influence of risk factors on behavior in children of women in OMT could aid the development of effective treatment guidelines and intervention programs for pregnant opioid-dependent women and their children. In the present paper, we test three different models that can be used to assess the influence of central risk factors.

Teratogenic Risk Model

Several theoretical and empirical studies have claimed that prenatal exposure to methadone or buprenorphine in combination with lifestyle-related factors such as maternal smoking and illicit drug use during pregnancy directly influence child development (for reviews, see Farid, Dunlop, Tait, & Hulse, 2008; Konijnenberg & Melinder, 2011). Prenatal exposure to opioids such as methadone and buprenorphine causes neonatal abstinence syndrome (NAS) in approximately half of all prenatally-exposed infants (Jones et al., 2010). While both methadone and buprenorphine act by binding to opioid receptors in the central nervous system, methadone is a full mu-opioid agonist while buprenorphine is only a partial mu-opioid agonist (Robinson, 2002). Buprenorphine has been associated with less severe NAS from that observed with methadone; this may be due to lower placental transfer of buprenorphine compared to methadone (Nanovskaya, Deshmukh, Brooks, & Ahmed, 2002). Infants born with withdrawal effects are likely to experience severe stress which, over a period of time, could lead to neuron loss and HPA dysregulation (McEwen & Sapolsky, 1995). Consequently, NAS may be associated with negative long-term consequences for children. In addition to NAS, it has been suggested that OMT during pregnancy may directly affect brain neurotransmission. For example, animal studies with rats have demonstrated that prenatal methadone exposure decreases serotonin uptake in the cortex and hippocampus which, due to its role in neural proliferation, differentiation, migration, and synaptogenesis could affect embryonic and fetal development (De Montis, Devoto, Angioi, Curreli, & Tagliamonte, 1983). Another rat study, showed that prenatal exposure to opioids reduced dopamine concentrations in the forebrain and striatum which, due to its influences on neurite outgrowth and branching, could disturb normal brain development (McGinty & Ford, 1980) (Lankford, DeMello, & Klein, 1988; Todd, 1992). Other OMT lifestyle-related factors may also contribute to a higher risk of developing problems in children of women in OMT. For instance, the majority of women in OMT continue to smoke during pregnancy, thus most children of mothers in OMT are prenatally exposed to nicotine (Jones et al., 2009), which may impair children's development by affecting cells in the hippocampus and somatosensory cortex (Castellanos & Tannock, 2002). Among pregnant women in OMT, a large proportion continues to use illicit drugs such as heroin, cocaine, or benzodiazepines during pregnancy (Kashiwagi, Arlettaz, Lauper, Zimmermann, & Hebisch, 2005; McCarthy, Leamon, Parr, & Anania, 2005). These drugs may have a negative effect on brain development, behavior, and cognition (Moe, 2002; Slinning, 2004; Walhovd et al., 2007). Several studies support the teratogenic risk model in that they link prenatal drug exposure to developmental problems, specifically problems in cognition (Baar & Graaff, 1994; Bauman & Levine, 1986; Konijnenberg & Melinder, 2014;

Melinder, Konijnenberg, & Sarfi, 2013; Salo et al., 2009). However, whether the teratogenic risk model can account for behavioral problems commonly found in children of women in OMT remains to be investigated. In this study the teratogenic risk model is used to investigate the relative effect of prenatal risk factors, such as prenatal drug use, on behavior problems in children of women in OMT.

Maternal Risk Model

Many patients in OMT have co-occurring psychiatric problems. In a study of 222 patients in OMT, 73% had some degree of current depression and 51% suffered from anxiety (Darke, Swift, & Hall, 1994). The prevalence was even higher for women; 82% suffered from depression and 66% from anxiety. A large proportion of parents in OMT (81%) use heroin several times a week or more on a regular basis. , and physical health problems are common, for example, in a study of 192 methadone patients 47% reported one or more physical health problems, most commonly hepatitis C (Senbanjo, Wolff, & Marshall, 2007). Women in OMT may also have concerns about the health of their baby and their ability to cope with motherhood and consequently may experience more pregnancy-related anxiety compared to other women. The fact that women in OMT often struggle with illicit drug use, mental health and/or physical problems can have implications for their children's development. Inequalities in women's health is a major contributor to behavior problems in children (Kahn, Zuckerman, Bauchner, Homer, & Wise, 2002). Child-parent interactions may be influenced by past and present drug use, as well as psychological and physical health. Parents who are drug dependent might be less attentive to the needs of their child due to the effects of the drugs on the parent's mental state. Further, maternal mental health problems such as depression may also affect child behavior. Depression in mothers is associated with negative parenting practices and maladaptive cognitions and affect which can adversely affect child behavior (Goodman, 2007). OMT in itself can also affect the parent-child relationship. For example, infants prenatally exposed to opioids are often less responsive to social interactions and difficult to comfort during the first few weeks of life, which may compromise the relationship with the primary caregiver (Dawe, Harnett, Staiger, & Dadds, 2000). Further, mothers in OMT are more likely to feel inadequate as parents and may experience feelings of guilt for exposing their infant to opioids in utero. These feelings can be reinforced by negative reactions from family members and medical staff, and it can be difficult for the mother to form a positive relationship with her child and maternal stress is likely to increase (Deren, 1986). Maternal mental and physical health problems may therefore increase the likelihood that children develop behavior problems. Behavior problems can in turn place additional stress on the parent-child relationship, starting a vicious cycle of negative parent-child interactions (Baker et al., 2003). In this study, the maternal risk model is used to investigate the contribution of maternal physical and psychological well-being and current drug abuse on behavior problems in children of women in OMT.

In this paper, the relative influence of the teratogenic risk model and the maternal risk model are tested. The basic relationships proposed in each model were investigated in order to determine the relative contribution of different risk factors, both prenatal and postnatal, on child behavior problems in children born to women in OMT. In addition, a third model was tested in which the teratogenic and maternal risk factors were investigated together in a combined model since these factors may interact together to influence child behavior.

Methods

Participants

The study cohort comprised of 35 children of women in OMT, 24 were prenatally exposed to methadone (mean age =52.24 months, SD = 1.82) and 11 to buprenorphine (mean age = 52.11 months, SD = 1.43). All children were enrolled in a prospective longitudinal study and had been followed up since birth (Bakstad, Sarfi, Welle-Strand, & Ravndal, 2009). All pregnant women in OMT in Norway who had a pregnancy due date in the time period January 2005 and January 2007 were invited to participate in the prospective study. The women were recruited from OMT centers throughout Norway. The women had been in OMT on average two and half year before they became pregnant with the child followed in this study. The cohort is described in greater detail elsewhere (Bakstad et al., 2009; Konijnenberg & Melinder, 2013; Lund, Brendryen, & Ravndal, 2014; Lund et al., 2012). Demographic and birth characteristics are listed in Table 1. The study was approved by the regional committee for medical and health research ethics and was conducted in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all subjects prior to participation. Participants received a gift certificate worth approximately 12 euro for participating.

Measures

Child Behavior Checklist/1,5-5 (CBCL; Achenbach, 1991). This checklist obtains reports from parents who describe specific behavioral, emotional, and social problems in preschool children. The checklist contains 99 items, which are scored on seven subscales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior). Scores were combined into two higher order scales; internalizing and externalizing problems. Scores were transformed to *T*-scores, with higher scores indicating more behavior problems. While scores ≤60 are within the clinical range, scores of 55 or above on the aggressive behavior and attention problem scales can be considered problematic. *Parenting Stress Index* (PSI; Abidin, 1990). The PSI is screening and diagnostic assessment designed to measure the relative magnitude of stress in the parent-child relationship. The PSI consists of 120 items and yields a Total Stress Score, a life stress score, and scale scores for both Child and Parent Characteristics, which pinpoint sources of stress within the family. High scores in the

child domain (> 122) reflect child characteristics that increase the difficulty associated with parenting. High scores in the parent domain (>153) suggest that the sources of stress and potential dysfunction of the parent-child system may be related to dimensions of the parent's functioning. High scores on the life stress scale (>16) indicates that the parent is experiencing high levels of stress outside the parent-child relationship.

Hopkins Symptom Checklist-25 (HSCL-25; Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974). The HSCL-25 is a screening tool used to diagnose elevated symptoms of anxiety and depression. It comprises a 10-item subscale for anxiety and a 15-item subscale for depression. Items are scored from 0 (not at all) to 4 (extremely). Mean cumulative symptom scores above 1.0 for each subcategory are classified as being in the clinical range.

European Addiction Severity Index (EuropASI; Kokkevi & Hartgers, 1995). The EuropASI is a revised version of the Addiction Severity Index (ASI). It is a personal semi-structured interview designed for clinical and research purposes. Results provide information on substance use and substance-related problems. For this study we used the subareas 'drug and alcohol use' during the past year and 'medical status' during the last 30 days of the EuropASI.

Background Measures. Neonatal data, including gestational age, birth weight, birth length, head circumference, and NAS was obtained from each child's medical record at birth. NAS was assessed using the modified Finnegan neonatal abstinence score or the Lipsitz score (see also Bakstad et al., 2009). Maternal drug and alcohol use as well as methadone or buprenorphine dose during pregnancy was measured with a structured interview administered in the last trimester of pregnancy. In addition, maternal education, maternal employment, and the children's age, gender, and living situation (with biological mother or other caregiver) was recorded.

Procedure

Participants were contacted by letter and telephone. On arrival at the lab, participants were told about the study and invited to ask questions. The CBCL, PSI, and HSCL-25 questionnaires were filled out at in a quiet testing room. The EuropASI was administered by telephone by one of the researchers after the lab visit.

This study is one of several based on the cohort (Konijnenberg & Melinder, 2013, 2014; Konijnenberg & Melinder, 2015; Lund et al., 2012; Melinder et al., 2013; Sarfi, Smith, Waal, & Sundet, 2011; Sarfi et al., 2013). While not all mothers participated in interviews at the 4-year follow up, this is not likely to affect the representativeness of the sample, as described in a previous study on the cohort (Lund et al., 2014).

Data analysis

All data was analyzed using IBM SPSS Statistics software (version 20.0, SPSS, Inc., Chicago, IL). For the regression analyses assumptions of multicollinearity, homoscedasticity, and normally distributed errors were checked and verified. NAS was coded as 0 = no medical treatment required for NAS or 1 = medical treatment required for NAS. Maternal employment

was coded as 0 = not currently employed or 1 = currently employed in a part-time or full-time job. Maternal education was scored as a continuous variable ranging from 0-17 years. Five children were no longer living with their biological parents at the time of the four-year-old follow up study. For these children, PSI, HSCL-25, and EuropASI data was not analyzed. However, neonatal measures and CBCL scores were included in the analysis. Only two-tailed probabilities were used, and given the small sample statistical significance was defined at an alpha level of .05. Effect sizes were interpreted according to Cohen's (1988) guidelines (d = 0.20 is small; d =0.50 is moderate; d = 0.80 is large). Preliminary analysis revealed that birth weight, birth length, head circumference, and gestational age were strongly correlated (all $r > .70$). To avoid problems of multicollinearity, only birth weight was included in the regression analyses since it was related to all other variables and had the highest predictive value. Preliminary analysis furthermore revealed no gender differences; gender was therefore not included as a variable in subsequent analyses.

Results

Demographics and Descriptive Statistics

Demographic, birth, and substance exposure characteristics are shown in Table 1. There were significantly more girls in the buprenorphine group compared to the methadone group. Further, on average, women in the buprenorphine group smoked more cigarettes per day during their pregnancy than women in the methadone group. No significant differences were found between the methadone and buprenorphine group on reported measures of child emotional and behavioral problems (CBCL), parenting stress (PSI), maternal anxiety and depression (HSCL-25), and maternal drug use during the past year (EuropASI). All mean scores on the CBCL, PSI, and HSCL-25 were within the normal range for both groups (Table 2). Since not all participants were available on telephone for the interview, response rates for the HSCL-25 and EuropASI were lower than for the PSI and CBCL. The methadone group scored above 55 on the CBCL subscales withdrawn problems and aggressive behavior problems and the buprenorphine group scored above 55 on the somatic complaints which could be indicative of problem behavior (Hudziak, Copeland, Stanger, & Wadsworth, 2004). Large standard deviations in CBCL scores suggest that there is considerable variation in behavior problems among the children. Moreover, 26% of all children had one or more scores in the clinical range (≥60) on the CBCL subscales. Since no differences were found on the CBCL, PSI, HSCL-25, and EuropASI scores between the methadone and buprenorphine exposed children, the two groups were combined for the remaining analyses.

CBCL Correlations

The Pearson correlations between parent ratings of child behavior, neonatal data, stress in the parent-child system, maternal anxiety, depression, drug use, and maternal health are reported in Table 3. In general, these correlations demonstrated a positive relationship between maternal perceptions of child behavior problems and the degree of stress reported by mothers. Further, child internalizing problems was moderately but significantly correlated with maternal physical problems and maternal drug use during the past year. Child externalizing problems was also correlated with maternal drug use during the past year as well as maternal depression. Maternal OMT dose during pregnancy was related to NAS. Maternal drug use during the past year was associated with child behavior problems, maternal stress, and depression.

Testing the Teratogenic, Maternal Risk, and Combined Model

To determine which factors contributed most to CBCL scores, three different models were tested using hierarchical multiple regression analysis (see Table 4). In all three models, variables were entered in two steps. In the first step, four demographic variables, children's age, birth weight, maternal employment, and maternal education, were entered to control for the potential relationship between these factors and the CBCL scores. In the second step of the hierarchical regression, the variables of relevance to the specific model were entered.

In the first model, the teratogenic risk model, the variables abstinence at birth, (standardized) dose of methadone or buprenorphine, exposure to other drugs, and average number of cigarettes smoked per day during pregnancy were entered in the second step. Two separate analyses were performed for each model, one for internalizing and one for externalizing problem scores. The teratogenic risk model did not account for a significant proportion of variance in reported internalizing or externalizing problems (R^2 = .27, p = .39 and R^2 = .33, p = .22, respectively).

In the second model, the maternal risk model, the variables maternal stress (PSI), anxiety and depression (HSCL-25), drug use (EuropASI), and physical problems (EuropASI) were entered in the second step. The maternal risk model accounted for a significant amount of the overall variance in reported internalizing and externalizing problems (R^2 = .59, p = .02 and R^2 = .65, p = .02, respectively).

In the third model, the combined model, the variables maternal stress (PSI), substance use (EuropASI), physical problems (EuropASI), depression (HSCL-25), and OMT dose during pregnancy were entered in the second step. These variables were chosen because they were correlated to child internalizing/externalizing problems (Table 3) or because they were significant predictors in the first or second model (Table 4). The combined model accounted for a significant amount of the overall variance in reported internalizing and externalizing problems (R^2 = .65, p = .008 and R^2 = .74, p = .003, respectively).

Discussion

Knowledge about the relative contribution of different risk factors, such as prenatal drug exposure, maternal health, and maternal stress, on children's behavior is important in order to provide the best possible care both for opioid dependent mothers and their children. The present study investigated reported child behavior problems in a cohort of 4-year-old children prenatally exposed to methadone or buprenorphine and used the teratogenic risk model, the maternal risk model, and a combined model to investigate the influence of different risk factors.
While the women generally reported few behavior problems in their children, there was a large variation in reported problem behavior on the CBCL; more than one-fourth of all children had one or more scores in the clinical range. Of the three models tested, support was obtained for two, the maternal risk model and the combined model. The teratogenic risk model did not receive support in the present study. The combined model, which included both pre- and postnatal risk factors predicted child behavior outcomes the best of the three models. These findings support the idea that a combination of pre- and postnatal factors influences the behavior of children of women in OMT.

Maternal stress was found to predict internalizing problems. This relationship between parenting stress and child behavior has been well documented (Abidin, 1990). High scores on the PSI have been associated with child behavior problems such as conduct disorder (Kazdin, 1990), hyperactivity (Beck, Young, & Tarnowski, 1990), and attention deficit disorder (Barkley, Fischer, Newby, & Breen, 1988). It has been suggested that while parental stress among substance-dependent mothers is related to child behavioral outcomes (Killeen & Brady, 2000), residential treatment can improve the ability to function in the parenting role. This in turn has a positive effect on children's behavior and suggests that dysfunctional behavior in children of drug-dependent women can be reversed with appropriate interventions focusing on the mother-child relationship (Killeen & Brady, 2000). Compared to drug-abusing mothers, the women in this study reported relatively few child behavior problems, and low levels of parenting stress, psychological and physical problems (Kelley, 1992; Soepatmi, 1994). This might indicate that the maintenance treatment they receive has a positive effect on their everyday functioning, which in turn positively affects child outcomes. The majority of the women received OMT before (sometimes years) they got pregnant. Accordingly, many had come far in their rehabilitation process. This may explain why, on average, few behavioral and psychological problems were reported. As mentioned before however, there were large variations in reported problems, suggesting that some families were coping better than others.

Maternal health and drug use was found to be related to child behavior problems. While the exact mechanisms through which maternal health and drug use affects child behavior problems are still uncertain, it has been proposed that the absence of a positive mother-child relationship, poor parenting, family disharmony, and the modeling of ineffective coping strategies may play a role (Foster, Garber, & Durlak, 2008). Further, since maternal health was associated with parenting stress, maternal health may affect child externalizing and internalizing symptoms by affecting maternal stress levels. Finally, since genetic factors play an important role

in psychopathology, children may have inherited their problem behaviors (Rutter, Moffitt, & Caspi, 2006).

OMT dose during pregnancy was found to predict child behavior problems. There are several explanations for this finding. One may be that OMT exposure during pregnancy directly influences child behavior problems at 4 years. This would suggest a direct teratogenic effect of prenatal methadone/buprenorphine exposure. Another possibility is that OMT dose influences child behavior indirectly. It is not unlikely that mothers who receive very high OMT doses during pregnancy are those who struggle the most with their addiction and consequently may expose their children to more adverse postnatal environments, which in turn negatively affects child behavior problems. The finding that the combined model, but not the teratogenic risk model predicted child behavior outcomes argues for the second interpretation. However, our findings cannot exclude the possibility that prenatal OMT exposure may have teratogenic effects on child development.

It is important to consider the direction of influence in the associations between maternal risk factors and children's behavior problems. Rather than simply attributing child internalizing and externalizing behavior problems to parental dysfunction, it is likely that the association is bidirectional, as the presence of behavioral problems may be a stressor for parents, which in turn may affect parental well-being (Connell & Goodman, 2002). It should also be noted that discussing the effects of drug-exposure on children's development is not an either/or debate among different models. There is increasing evidence that prenatal drug exposure can affect child development through several pathways, and that evidence for one mechanism does not exclude other mechanisms of actions as supported by our finding that the combined model best predicted child behavior problems (Fisher et al., 2011; Konijnenberg & Melinder, 2011).

Several limitations need to be considered. Much information collected for this study was based on maternal self-report, which could result in inaccurate or socially desirable reporting. While drug and alcohol use may be underreported in self-report measures, the results from frequent urine controls during pregnancy suggests otherwise, as they were generally in agreement with self-report measures (Bakstad et al., 2009). Because both the outcome measure (CBCL) and independent maternal variables were mainly based on self-report, results may have been affected by similarities in the way the mothers responded on these questionnaires. While the sample size was small, a common limitation in studies on long-term effects of prenatal methadone and buprenorphine exposure (Konijnenberg & Melinder, 2011), the study included 74% of all children known to have been exposed to methadone or buprenorphine during pregnancy born in Norway in the period 2005-2006. The sample is therefore highly representative for children of women in OMT in Norway. Strengths of the study include fewer confounding factors. Confounding factors such as poverty and homelessness, common in OMT populations (Tuten, Jones, & Svikis, 2003), is a less of a problem in the Norwegian setting; housing is paid for by the state for those who are unable to cover these costs themselves, including people with substance use and/or mental health problems, and all have the same access to the health care system which covers all inhabitants (Norwegian Directorate of Health, 2012). Thus, while the women in OMT

in Norway also typically represent low-income families, they or experience the same degree of poverty as in for example the U.S.

In conclusion, children prenatally exposed to methadone or buprenorphine were given scores within the normal range when assessed by the CBCL. While group means for children were within the nonclinical range, a number of mothers reported clinically significant child behavior problems, which appeared to be related to methadone/buprenorphine dose during pregnancy, maternal stress, and maternal drug use after pregnancy. These findings suggest that behavior problems in children of women in OMT may be a result of a combination of prenatal and postnatal risk factors. Intervention programs should therefore be targeted at decreasing maternal stress during pregnancy and after delivery and at promoting maternal health. Further, these findings indicate the need to study the effects of prenatal methadone and buprenorphine exposure on children's behavior within a developmental perspective, taking into consideration both direct and indirect effects.

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Table 1.*Demographic, birth, and substance use characteristics*

	Methadone (*n*=24)	Buprenorphine (*n*=11)	t/χ^2	*p*
Child characteristics				
Female, *n* (%)	8 (33.3)	8 (72.3)	4.72	.03*
Living with biological parent(s), *n* (%)	21 (87.5)	9 (81.8)	.20	.66
Birth weight, kg	3.11 (0.7)	3.2 (0.3)	-.45	.65
Birth length, cm	47.7 (3.5)	48.5 (1.4)	-.74	.46
Head circumference, cm	33.67 (2.3)	34.27 (1.7)	-.78	.44
Gestational age, weeks	38.7 (3.0)	39.6 (1.8)	.-.93	.36
Treated for NAS, *n* (%)	13 (54.2)	9 (81.8)	2.47	.12
Mother/guardian characteristics				
Age, years	36.0 (4.6)	36.5 (5.3)	-.28	.78
Education, years	12.0 (2.5)	12.1 (1.1)	.51	.61
Employment, *n* (% employed)	11 (45.8)	5 (45.5)	2.08	.15
Maternal substance use during pregnancy				
Tobacco, *n* (%)	23 (95.8)	11 (100.0)	2.25	.13
Tobacco, average amount of cigarettes per day	9.1 (5.7)	13.1 (5.3)	-2.06	.047*
Alcohol, *n* (%)	6 (25.0)	2 (18.2)	1.66	.20
Marijuana, *n* (%)	4 (16.7)	3 (27.3)	.53	.47
Amphetamine, *n* (%)	4 (16.7)	4 (36.4)	.20	.66
Benzodiazepine, *n* (%)	10 (41.7)	4 (36.4)	1.08	.30
Opioids (other than meth/bup), *n* (%)	4 (16.7)	3 (27.3)	.53	.47
Illegal drug use total, *n* (%)[a]	10 (41.7)	5 (45.5)	.09	.77
Mean methadone/buprenorphine dose at delivery, mg[b]	85.96 (62.6)[a]	12.73 (6.3)	-	-

Note. Values are given as mean (standard deviation) unless otherwise specified. For categorical variables, X^2-test was used; for continuous variables T-test was used. [a]Illegal drugs were defined as non-prescribed illegal substances. [b]One outlier (660 mg methadone) was not included in this mean. *p<.05

Table 2

Mean rating scores for the methadone and buprenorphine group at 4-years.

	Methadone	Buprenorphine	t/χ^2	*p*
CBCL	*n = 24*	*n = 11*		
Emotionally Reactive	54.67 (6.18)	51.64 (4.46)	1.46	.15
Anxious/Depressed	53.08 (3.97)	52.18 (2.86)	.68	.50
Somatic Complaints	52.54 (4.60)	55.09 (5.60)	-1.42	.16
Withdrawn	55.96 (6.87)	52.73 (4.05)	1.44	.16
Sleep Problems	54.13 (4.52)	54.18 (5.58)	-.03	.98
Attention Problems	54.46 (5.69)	51.91 (2.17)	1.43	.16
Aggressive Behavior	55.33 (9.92)	51.36 (2.98)	1.29	.21
Internalizing problems	49.67 (10.02)	49.18 (5.49)	.15	.88
Externalizing problems	50.54 (12.33)	45.27 (7.25)	1.31	.20
Total problems	50.42 (11.25)	47.18 (5.02)	.91	.37
PSI	*n = 21*	*n = 9*		
Child domain score	95.95 (20.94)	83.67 (13.08)	1.62	.12
Parent domain score	125.29 (25.49)	122.33 (24.04)	.30	.77
Life stress	3.14 (2.13)	3.22 (2.22)	-.09	.93
Total stress	221.23 (44.31)	206.00 (33.62)	.92	.37
HSCL-25	*n = 18*	*n = 9*		
Anxiety	.49 (.45)	.82 (.71)	-1.50	.15
Depression	.85 (.63)	.64 (.47)	.90	.38
EuropASI	*n = 16*	*n = 9*		
Alcohol (%)	7 (29.2)	2 (22.2)	1.16	.28
Heroin (%)	0	0	-	-
Benzodiazepine (%)	2 (12.5)	2 (22.2)	1.41	.52
Cocaine (%)	1 (6.3)	0	.59	.44
Amphetamine (%)	1 (6.3)	2 (22.2)	1.39	.24
Cannabis (%)	0	2 (22.2)	3.87	.05
Other drugs (%)	1 (6.3)	0	.59	.44
Illegal drug use total, *n* (%)[a]	4 (25.0)	3 (33.3)	.20	.66
Physical problems (%)	7 (43.8)	4 (44.4)	.001	.97

Note. For categorical variables, X^2-test was used; for continues variables T-test was used. PSI = Parenting Stress Index; CBCL = Child Behavior Checklist; SCL = Hopkings Symptom Check List; EuropASI = European Addiction Severity Index.[a] Illegal drugs were defined as non-prescribed illegal substances.

Table 3

Correlations between ratings of child behavior of 4 years old children and mother's reported stress, psychological problems, physical problems and maternal drug use

Variables	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
1. Internalizing problems (CBCL)	-									
2. Externalizing problems (CBCL)	.62**	-								
3. Abstinence	-.05	-.15	-							
4. OMT dose (pregnancy)	.12	.09	.40*	-						
5. Maternal substance use (pregnancy)	-.03	.04	-.32	-.048	-					
6. Cigarette smoking (pregnancy)	.14	.13	-.09	-.08	.16	-				
7. Total stress score (PSI)	.70**	.67**	-.07	.11	-.05	.28	-			
8. Maternal anxiety (HSCL-25)	.33	.28	.08	-.06	-.06	.21	.32	-		
9. Maternal depression (HSCL-25)	.35	.53**	-.07	.04	-.17	.13	.49**	.48**	-	
10. Maternal substance use - past year (EuropASI)	.44*	.49*	.41*	.13	-.22	-.12	.40*	.23	.44*	-
11. Maternal physical problems (EuropASI)	.45*	.33	-.14	-.05	-.23	.03	.43*	.38	.62*	.38

Note. CBCL = Child Behavior CheckList; PSI = Parenting Stress Index; HSCL = Hopkings Symptom Check List; EuropASI = European Addiction Severity Index * $p < .05$ ** $p < .01$

Table 4. *Hierarchical Multiple Regression Analyses Predicting Externalizing and Internalizing Behavior Problems in 4 year old children*

	Teratogenic risk model (model 1)				Maternal risk model (model 2)				Combined model (model 3)			
	Internalizing		Externalizing		Internalizing		Externalizing		Internalizing		Externalizing	
Predictor	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1	.09		.21		.09		.21		.09		.21	
Control variables[a]												
Step 2												
Teratogenic risk variables (model 1)	.17		.09									
Abstinence		-33		-.23								
Met/bup dose (pregnancy)		.50*		.37								
Other prenatal drug exposure		-.23		-.09								
Cigarette exposure (pregnancy)		.15		.15								
Maternal risk variables (model 2)					.55*		.44*					
Total stress score (PSI)						.58*		.28				
Anxiety (HSCL-25)						.06		.11				
Depression (HSCL-25)						-.14		.29				
Drug use past year (EuropASI)						.19		.33				
Physical problems (EuropASI)						.23		-.16				
Combined model variables (model 3)									.61**		.58**	
Met/bup dose (pregnancy)										.33		.44*
Total stress score (PSI)										.43		.06
Depression (HSCL-25)										-.16		.24
Physical problems (EuropASI)										.25		-.16
Drug use past year (EuropASI)										.29		.57*

Note. Control variables include age, birth weight, maternal employment, and maternal education. *$p < .05$. **$p < .01$.